UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,622	12/10/2004	Joan Roig Amores	MGH-006.1P US	2699

7590 05/08/2007

Leon R Yankwich
Yankwich & Associates
201 Broadway
Cambridge, MA 02139

EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
05/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,622	ROIG AMORES ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *4-7,9,10 and 17-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed 2/28/07 in response to the Office Action of 1/29/07 is acknowledged and has been entered.

Applicant's election with traverse of Group I, claims 1-16, and the species non-activated Nercc1 kinase for the form of Nercc1 kinase protein, non-activated Nek7 kinase or fusion protein thereof for the form of kinase substrate, detecting with an antibody for detecting the phosphorylated form of the kinase substrate, phosphorylated Nek7 kinase or fusion protein thereof for the form of phosphorylated kinase substrate, and microtiter plate for species of vessel is acknowledged and has been entered.

Election/Restrictions

Applicants traverse the finding of lack of unity based on WO99/66051 and argue that the claims are in fact so linked as to form a single general inventive concept consistent with PCT Rule 13.1 and possess a common special technical feature that fulfills the requirement for unity of invention in accordance with PCT Rule 13.2.

Upon review and reconsideration, the finding of lack of unity based on the finding of a lack of special technical feature for the claimed invention is hereby withdrawn.

However, upon review and reconsideration, it is found that the claimed inventions lack unity of invention because under PCT Rule 13.1 unity of invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

A) A product and a special process of manufacture of said product.

B) A product and a process of use of said product.

C) A product, a special process of manufacture of said product, and a process of use of said product.

D) A process and an apparatus specially designed to carry out said process.

E) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

The invention Groups and species are as previously set forth in the Office Action of January 29, 2007.

The invention of Group 1 is drawn to a cell free method of identifying a compound, as disclosed in the specification that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a Nercc1 kinase protein, and a kinase substrate, (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit the Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated kinase substrate in the presence and absence of said test compound, wherein a lower level of phosphorylated kinase substrate produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis.

The inventions of Groups 2-12 are drawn to methods that are different from that of Group 1 and combinations of methods are not proper and therefore Groups 2-12 do not have unity of invention with Group 1.

Although the invention of Group 13 is drawn to a product, this product is not used in the method of Group 1 and therefore Group 1 and 13 do not have unity of invention.

Thus all of the products and methods are properly broken out as separate groups and each of the claimed inventions relates only to a single general inventive concept, different one from the other.

Accordingly, Groups 1-13 are not so linked as to form a single general inventive concept and the finding of lack of unity is proper.

During a telephone conversation with Thomas R. Berka on April 16, 2007 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-16, and the species non-activated Nercc1 kinase for the form of Nercc1 kinase protein, non-activated Nek7 kinase or fusion protein thereof for the form of kinase substrate, detecting with an antibody for detecting the phosphorylated form of the kinase substrate, phosphorylated Nek7 kinase or fusion protein thereof for the form of phosphorylated kinase substrate, and microtiter plate for species of vessel. Affirmation of this election must be made by applicant in replying to this Office action.

2. Claims 1-45 are pending.

3. Claims 4-7, 9, 10, and 17-45 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 8, and 11-16, as drawn to a non-activated Nercc1 kinase, non-activated Nek7 kinase or fusion protein thereof, detecting with an antibody, phosphorylated Nek7 kinase or fusion protein thereof, and microtiter plate for species of vessel are currently under consideration.

Specification

5. The specification is objected to for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs: see figure 2A. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

6. The disclosure is objected to because of the following informalities:

The blank space from lines 1-7 must be deleted, because it cannot be determined if something was intended for this space in the application and is missing.

The identifying data of all prior applications for which benefits are claimed should be provided in either the first sentence(s) of the specification or in an application data sheet. See MPEP § 202.02

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 8, and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The term "a lower level" in claim 1 is a relative term, which renders the claim indefinite. The term "a lower level" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One of skill in the art cannot determine how much lower the level of phosphorylated kinase substrate, Nek7, must be for the mitosis inhibitor to be identified. Is a 1% lower level sufficient for identification of a mitosis inhibitor? Or is a 5% lower level sufficient? Or is some other lower level required for identification of a mitosis inhibitor? Thus the metes and bounds of the claims cannot be determined.

9. Claims 1-3, 8, and 11-16 are further rejected as being indefinite in the use Nercc1 and Nek7 as the sole means of identifying proteins used in the claimed method. The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to include the SEQ ID NO: of Nercc1 and Nek7 would obviate this rejection because a SEQ ID NO: is a unique identifier, which unambiguously define a given protein.

10. Claims 2, 3, 8, and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 3 are drawn to the method according to claim1, wherein the non-activated Nercc1 kinase protein is *initially* a non-activated Nercc1 kinase protein capable of auto-activation by auto-phosphorylation. The claims are indefinite because it is unclear how the Nercc1 kinase protein is "initially" non-activated. Are other kinases added to inhibit or activate the Nercc1 kinase? Does some other transformation occur that allows the initially non-activated kinase to become active? The metes and bounds of the claim of the claim cannot be determined from the construction of the claim and, thus the claims are indefinite. Amendment of the claim to delete the term "initially" will obviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1-3, 8, and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a cell free method of identifying a compound that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a Nercc1 kinase protein, wherein the Nercc1 kinase protein is a non-activated Nercc1 kinase protein, and a kinase substrate, wherein the kinase substrate is a non-activated Nek-7 protein, (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit the Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated Nek7, in the presence and absence of said test compound, wherein a lower level of phosphorylated Nek7 produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis.

The specification teaches that Nercc1 kinase was identified as a protein that interacts with and phosphorylates Nek6 by co-immunoaffinity purification, see Example 2 and 4. The specification teaches that the functions of other Neks are largely unknown, the function of Nek6 and the closely related Nek7, is to cooperate in the activation of p70 S6 kinase, see p. 4, lines 4-12. The specification teaches that the Neks are structurally related to NIMA, a protein kinase involved in the regulation of mitosis, see p. 2 lines 15-32 and p. 3 lines 1-20.

The specification teaches that the Nercc1 is phosphorylated in cultured HeLa cells during mitosis. The specification teaches that the mitotic kinase $p34^{Cdc2}$ phosphorylates Nercc1 *in vitro*, suggesting that $p34^{Cdc2}$ contributes to the phosphorylation of Nercc1 in mitosis, see

Example 9 and figure 5.

The specification teaches that transfection of inactive kinase mutant of Nercc1, K81M (see p. 46, lines 17-19) blocked cells from undergoing cell division and inducing a majority of cells to die, see Example 11, p. 55, lines 15-28. Additionally, the specification teaches that microinjection of cells with an anti-Nercc1 antibody prevented entry into mitosis, see p. 55, lines 29-33.

The specification teaches that Nercc1 could phosphorylate and activate Nek7 in an *in vitro* kinase assay, see p. 66 lines 1-25 and Figure 10. It appears that the phosphorylation and activation of Nek7 in mitotic cells, in cell culture or *in vivo*, has not been determined because the specification teaches that antibodies reactive with endogenous Nek7 have not been obtained, see p. 67, lines 16-17.

Additionally, the specification teaches that compounds that inhibit Nercc1 activity will inhibit a critical step in regulating and maintaining mitosis. The specification teaches that such compounds are candidates for use in treating conditions of uncontrolled mitotic progression, such as in cancer and/or eukaryotic microbial infections (e.g., by fungi, parasitic protozoa, parasitic helminths), see p. 4 lines 26-30

Thus, in view of the above, the claims read on identifying compounds for identifying inhibitors of mitosis that will treat cancer and/or eukaryotic microbial infections.

One cannot extrapolate the teachings of the specification to the scope of the claims because no nexus has been established between the Nercc1 kinase activity, level of phosphorylation of Nek7 and inhibition of mitosis and because 1) the phosphorylation of a substrate by Nercc1 does not predictably extrapolate to an effect of that phosphorylated substrate

on mitosis 2) the unpredictability of cancer therapeutic development is well known in the art 3) there is no teaching in the specification or art of record that either Nercc1 kinase or Nek7 is expressed in eukaryotic microbes.

1) As drawn to the regulation of mitosis by Nercc1 phosphorylated substrates, Holland et al. (J. Biol. Chem., 2002, 2777:16229-16240) teach that Nek8 (which Roig et al in Genes & Dev. July 1, 2002, 16:1640-1658, IDS, teach has an identical sequence to Nercc1, see p. 1643, left col.) phosphorylates Bicd2 *in vitro* and associates with Bicd2 in cultured cells, see Abstract and Fig. 6. Holland et al. teach that Bicd2 localizes to cytoskeletal structures, and its subcellular localization is dependent on microtubule morphology. Holland et al. teach that treatment of cells with nocodazole leads to dramatic reorganization of Bicd2 and correlates with Nek8 phosphorylation. Holland et al. teach that this may be indicative of role for Nek8 and Bicd2 associated with cell cycle *independent* (emphasis added) microtubule dynamics, see Abstract, p. 16240, left col., and Fig. 7 and 8.

Although Nercc1 is phosphorylated and activated during mitosis (see Figs. 5, 13, and 14) and phosphorylates Nek7 *in vitro*, however, given that no data is presented that Nek7 is phosphorylated in mitosis by Nercc1 or any other kinase and given that Nercc1 phosphorylates substrates that do not appear to have an effect on mitosis, such as Bicd2, given that the specification and the art of record do not establish a nexus between phosphorylated Nek7 and mitosis or Nercc1 phosphorylation of Nek7 and mitosis, given that Nercc1 has multiple substrates, and given that Nercc1 substrates have different functions (some of which do not appear to be related to mitosis), one of ordinary skill in the art would not reasonably predict that a cell free assay that measures Nercc1 phosphorylation of Nek7 would predictably identify an

inhibitor of mitosis given the lack of predictable nexus between Nercc1, Nek7 phosphorylation, and mitosis. Thus, undue experimentation would be required for one of ordinary skill in the art to establish a nexus between Nercc1 phosphorylation of Nek7 and mitosis.

2) As drawn to the unpredictability of the development cancer treatments, in particular, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, although many thousands of drugs have shown activity in either cell or animal models, only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para.

Given the unpredictability of identifying cancer therapeutics and given that neither the specification nor art of record has established any nexus between lowering Nercc1 kinase phosphorylation of Nek7 and cancer, one of skill in the art could not predictably use the claimed method for identification of compounds for the treatment of cancer. Thus in the absence of data in appropriate animal models showing a lower level of Nek7 phosphorylation by Nercc1 relates to the treatment cancer, one of skill in the art would not be able to predictably use the clamed invention without undue experimentation.

3) As drawn to the unpredictability of identifying compounds that treat eukaryotic microbial infections using the claimed method, neither the specification nor the art of record shows any data on the expression, activity, interaction, or phenotypes associated with Nercc1 kinase or Nek7 in eukaryotic microbes, nor is any nexus established between Nercc1 kinase

activity, phosphorylated Nek7, and mitosis in eukaryotic microbes. Thus, given the above, one of ordinary skill in the art could not predictably make and use the invention without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

12. If applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph Claims 1-3, 8, and 11-16 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a non-activated Nercc1 kinase protein, **wherein the Nercc1 kinase protein is SEQ ID NO: 2**, and a kinase substrate, wherein the kinase substrate is **SEQ ID NO: 6** , (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit said Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated **SEQ ID NO: 6** in the presence and absence of said test compound, wherein a lower level of phosphorylated **SEQ ID NO: 6** produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis, *does not* reasonably provide enablement for a method of identifying a compound that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a non-activated Nercc1 kinase protein, and a kinase substrate, wherein the kinase substrate is a non-activated Nek-7 protein, (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit the Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated Nek7 in the presence and absence of said test compound, wherein a lower level of phosphorylated Nek7 produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of identifying a compound that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a non-activated Nercc1 kinase protein, and a kinase substrate, wherein the kinase substrate is non-activated Nek7 protein (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit the Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated Nek7 in the presence and absence of said test compound, wherein a lower level of phosphorylated Nek7 produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis.

This means that the claimed method will be able to identify a compound that is an inhibitor of mitosis using a kinase reaction mixture comprising *any* Nercc1 kinase protein or *any* non-activated Nek7protein.

The specification teaches as set forth above.

Additionally, the specification teaches that **a** (emphasis added) wild type Nercc1 has the 979 amino acid sequence of SEQ ID NO: 2 and that **a** (emphasis added) Nek7 has the amino acids of SEQ ID NO: 6, see p. 23, lines 25-28 and para. bridging p. 23-24.

The specification teaches that in addition to wild type Nercc1 and Nek7 proteins, a variety of fusion proteins and mutant variants of these wild type kinase proteins are useful in compositions and methods of the invention, see p. 24, lines 3-5.

The specification teaches that the terms "polypeptide" or "protein", as used herein, comprise a linear polymer of two or more amino acid residues linked by peptide bonds. The term "peptide" is used herein to refer to relatively short polypeptides, especially polypeptide having 20 or fewer amino acids. The specification teaches that "Protein" may be synonymous with a single "polypeptide" or "peptide" or may comprise more than one "polypeptide" or "peptide" as in a dimeric or other multimeric protein, see p.20, lines 23-28.

The specification teaches that a Nercc1 kinase useful in the invention is any molecule that provides functional Nercc1 activity, including, but not limited to, wild type Nercc1 kinase protein (e.g., having the amino acid sequence), enzymatically active mutant variants of Nercc1 kinase, and enzymatically active fusion proteins comprising all or a portion of Nercc1 kinase, as described or exemplified herein, see p. 23 lines, 14-18.

Furthermore, the specification teaches that a protein, polypeptide, and peptide

homologues within the scope of the present invention will be about 70%, preferably about 80%, and more preferably about 90% or more (including about 95%, about 97%, or even about 99% or more) homologous to a Nercc1 kinase as disclosed herein, see p. 23 lines, 4-10.

One cannot extrapolate the teachings to the scope of the claims because the teaching of the specification teaches that the Nercc1 kinase protein or Nek7 protein of the claimed method are inclusive of a myriad of variants of the Nercc1 kinase protein or Nek7 protein and the specification has not established a nexus between all of these variant forms of Nercc1 kinase and Nek7 and mitosis. Furthermore, one of skill in the art could not predictably establish a nexus between all of the Nercc1 and Nek7 variants envisioned in the specification and mitosis because of known unpredictability of predicting function from structure in protein biochemistry.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a

sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for the

inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col. 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col. 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by Pero et al. (US PG Pub 20030105000) who specifically teach on page 73 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similarity to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity or similarity alone cannot be used to predict the function of a protein.

Given not only the teachings of Bowie et al, Lazar et al, Burgess et al, Scott et al. and Pero et al. but also the limitations and pitfalls of using computational sequence analysis taught by Bork clearly the ability of all of the variants of the Nercc1 kinase protein and Nek7 encompassed

by the claims and contemplated by the specification to regulate mitosis could not be predicted, based on sequence similarity to SEQ ID NO: 2 or SEQ ID NO: 6, respectively. Furthermore, given the above, one of skill in the art could not reliably predict that a method using the variants of Nercc1 or Nek7 contemplated in the specification in the method of claim 1 would predictably identify a compound that is an inhibitor of mitosis. Given the above, it is clear that undue experimentation would be required of one of skill in the art to make and use the full scope of Nercc1 kinase and Nek7 proteins that regulate mitosis encompassed by the claims in the claimed method. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

13. Claims 1-3, 8, and 11-16 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-3, 8, and 11-16 are broadly drawn to a method of identifying a compound that is an inhibitor of mitosis comprising the steps of: (a) providing a kinase reaction mixture comprising a purine nucleoside triphosphate, a non-activated Nercc1 kinase protein, and a kinase substrate, wherein the kinase substrate is non-activated Nek7 protein, (b) incubating said kinase reaction mixture in the presence and absence of a test compound for a time sufficient to permit the Nercc1 kinase protein to phosphorylate the kinase substrate, and (c) determining the level of phosphorylated Nek7 in the presence and absence of said test compound, wherein a lower level of phosphorylated Nek7 produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis.

The state of the art is such that it is well know in the art that protein biochemistry is unpredictable and, thus, predicting protein function from structure is unpredictable. In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry

out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Thus, given the above, it is clear that in the protein biochemistry arts an adequate written description is essential for one of skill in the art to make and use the claimed invention.

Given the above and given that the specification teaches that in addition to wild type Nercc1 and Nek7 proteins, a variety of fusion proteins and mutant variants of these wild type kinase proteins are useful in compositions and methods of the invention, see p. 24, lines 3-5, it is clear that the specification does not provide a written description of the broadly claimed invention for the reasons set forth below Additionally, given the above and given that the

specification teaches that a Nercc1 kinase useful in the invention is any molecule that provides functional Nercc1 activity, including, but not limited to, wild type Nercc1 kinase protein (e.g., having the amino acid sequence), enzymatically active mutant variants of Nercc1 kinase, and enzymatically active fusion proteins comprising all or a portion of Nercc1 kinase, as described or exemplified herein, see p. 23 lines, 14-18. Furthermore, the specification teaches that a protein, polypeptide, and peptide homologues within the scope of the present invention will be about 70%, preferably about 80%, and more preferably about 90% or more (including about 95%, about 97%, or even about 99% or more) homologous to a Nercc1 kinase as disclosed herein, see p. 23 lines, 4-10 it is further evident that the specification does not provide a written description of the broadly claimed invention for the reasons set forth below.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or

> recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not

adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis, per Lilly by structurally describing a representative number of non-activated Nercc1 kinase proteins or non-activated Nek7 proteins that can be used to identify an inhibitor of mitosis, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis, nor does the specification provide any partial structure of such polypeptide, nor any physical or chemical characteristics of a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO: 2 and SEQ ID NO: 6, this does not provide a description of a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis that would satisfy the standard set out in Enzo.

The specification also fails to describe a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis by the test set out in Lilly. The specification describes only SEQ ID NO: 2 and SEQ ID NO: 6. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis that is required to practice the claimed invention. Since the specification fails to adequately describe the products upon which the methods depend, it also fails to adequately describe their method of use.

Although the prior art describes Nercc1, Nek8 in Holland et al. (see above), and Nek7 (see Belham et al., Current Biology, 2001, 11:1155-1167, IDS) this does not provide an adequate written description of a non-activated Nercc1 kinase protein or non-activated Nek7 protein that can be used to identify an inhibitor of mitosis that is required to practice the claimed invention given the multiple variants of said proteins contemplated in the specification.

Closest Prior Art

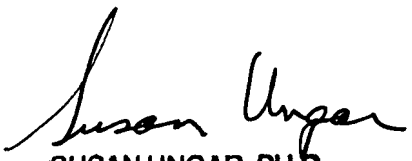
14. The closest prior art is Holland et al. (J. Biol. Chem., 2002, 2777:16229-16240). Holland et al. teach that Nercc1 (Nek8, see above) is a kinase and examine its role in the cell cycle. However, Holland et al. teach away from Nercc1 (Nek8) having a role in the cell cycle in general or mitosis in particular, see Abstract, Figs. 7 and 8 and last pargraph, p. 16240. Holland et al. does not teach that Nek7 is a substrate of Nercc1.

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

Notice to Comply	Application No. 10/517,622	Applicant(s) Amores et al.	
	Examiner Peter J. Reddig	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The disclosure is lacking numerous sequence identifiers and sequence ID numbers, see the section titled "Sequence Listing" in the accompanying First Office Action on the Merits.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, DC 20231
www.uspto.gov

APPLICATION NO. /CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/517,622	12/10/2004	Joan Roig Amores	MGH-006.1P US

EXAMINER	
Peter Reddig, Ph.D.	
ART UNIT	**PAPER**
1642	

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must provide the appropriate SEQ ID NO: for all sequences encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

If a complete reply has not been submitted by the time period set in the accompanying Office action has expired, this application will become abandoned under 37 CFR 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (http://ww.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual-ePAVE)

2. Mailed to

Mail Stop Sequence

Commissioner for Patents

P.O. Box 22313-1450

Alexandria, VA 22313-1450

3.Hand Carry, Federal Express, United Parcel Service or other delivery service to:

U. S. Patent and Trademark Office

Mail Stop Sequence

Customer Window

Randolph Building

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Reddig whose telephone number is 571-272-9031. The examiner can normally be reached on M-F 8:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foleycan be reached on 571-272-0890.

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter Reddig, Ph.D.
Art Unit 1642